DOCKET NO.: ISIS0052-100 (ISPH-0622) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: Miraglia, Nero, Graham, Monia, Koller, Chiang, and Manoharan

Serial No.: 10/005,344 Group Art Unit: 1635

Filed: December 4, 2001 Examiner: T. Gibbs

Title: Antisense Modulation Of Human MDM2 Expression

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION UNDER 37 CFR §1.132

Sir:

I, C. Frank Bennett, a citizen of the United States, residing at 1347 Cassins Street, Carlsbad, California 92009, do declare and state that:

1 I am the Vice President of Antisense Research at ISIS Pharmaceuticals, Inc., the assignee of the above-identified patent application. I hold the degree of Ph.D., and have been employed by the assignee of this application since 1989. I am an expert in the art of antisense technology.

2. I have read the Office Action dated November 12, 2003 and understand that the claims of this invention have been rejected as allegedly being anticipated by 35 U.S.C. §102(b) or allegedly made obvious under 35 U.S.C. §103(a) by the following references, or combinations thereof: Landers *et al.*, *Cancer Res.*, 1997, *57*, 3562-3568 (Landers), International Application No. WO 93/20238 (Burrell), Branch, *TIBS*, 1998, *23*, 45-50 (Branch), U.S. Patent No. 5,872,242 (Monia), and U.S. Patent No. 6,172,216 (Bennett). In addition, the statements throughout the Office Action regarding the alleged reasonable expectation of success by one of skill in the art

for inhibiting the expression of any particular gene or mRNA with oligomeric compounds based upon results achieved with another gene or mRNA are unsupported and incorrect.

3. It is not possible to currently predict the level of inhibition of expression achieved with an oligomeric compound prior to carrying out the appropriate experiments. For instance, if one skilled in the art achieved at least 60% inhibition in the expression of a first gene or mRNA with oligomeric compounds that are specific to the first gene or mRNA, one skilled in the art would not have any expectation of success in achieving at least 60% inhibition in the expression of a different gene or mRNA with a different set of oligomeric compounds that are specific to the different gene or mRNA. The level of inhibition of expression that is observed for one target has no bearing on the level of inhibition of expression expected for a different target.

4. For example, as indicated by Exhibits A (inhibition of human tyrosine kinase, non-receptor, 1 mRNA expression in T-24 cells) and B (inhibition of rat urate anion exchanger 1 mRNA expression in Rin-M cells), over 75 oligomeric compounds were examined for their ability to inhibit expression (please note that the results are presented as % expression of the control). None of the oligomeric compounds tested inhibited expression by at least 60%. This is true for a number of genes. It is never possible to predict before the appropriate experiment is performed, what oligomeric compounds will generate the desired level of inhibition of expression.

5. This evidence demonstrates that one skilled in antisense oligonucleotide screening cannot, *a priori*, expect a high level of inhibition (i.e., such as at least 60%) of a gene or mRNA simply by observing the same high level of inhibition for a different target. The statements in the Office Action are neither accurate nor capable of being supported by the facts of oligonucleotide screening.

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6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 4-23-04 By: C. Frank Bennett

C. Frank Bennett, Ph.D.